REMARKS

The indication of allowable subject matter is respectfully acknowledged.

The Amendments

Claims 1-5 are amended to address the objection thereto and correct another grammatical error. The amendments do not narrow the scope of the claims and/or were not made for reasons related to patentability. The amendments should not be interpreted as acquiescence to any objection or rejection made in this application.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 8, 9 and 14 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement, is respectfully traversed.

Applicants urge that the original disclosure – taken in view of the knowledge of one of ordinary skill in the art – provides sufficient guidance for one of ordinary skill in the art to carry out the claimed methods.

The PTO does not dispute that applicants have provided a sufficient showing that a representative sample of the claimed compounds:

- exhibit PDE9A-inhibiting activity (results of the assays at pages 17-19),
- provide for increase in intracellular neuronal cGMP concentration in cell cultures (pages 19-20 of applicants' specification),
- provide for long term potentiation regarded as a cellular correlate of learning and memory processes (pages 20-21 of applicants' specification), and
- lead to advantageous results in the social recognition test (pages 21-22 of applicants' specification).

Applicants have provided examples of literature references which show the acceptance in

the art that there is a nexus between these properties and use in carrying out the claimed methods, i.e., treating an impairment of learning and/or memory, particularly connected with Alzheimer's disease or the other specific conditions in claim 14. This discussion of the nexus is re-emphasized and expanded on in the following paragraph. Applicants also attach herewith an additional literature reference supporting this position (Van der Staay, *Neuropharmacology*, vol. 55, pp. 908-918 (2008), included in the discussion below). Applicants have thus provided a great deal of evidence in support of enablement. In contrast, the PTO has provided no evidence to support why it doubts the truth or accuracy of the inventors' statements that the invention can be used as described in the disclosure and no evidence which shows an inconsistency in the disclosure or in applicants' evidence of record which supports the case for enablement. In this context, it is pointed out that, in order to support a rejection under 35 U.S.C. §112, first paragraph, for lack of enablement, the burden lies first with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims. See, e.g., MPEP §2164.04 citing In re Marzocchi et al., 169 USPQ 367 (CCPA 1971), which states:

> ".. a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein..",

and further,

> "..it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." (emphasis original).

Applicants urge that the evidence of record fails to support the PTO's burden of proof on the rejection. To the contrary, the actual evidence of record is all in support of applicants' position.

The evidence of record supports that one of ordinary skill in the art would have a reasonable expectation that compounds having the activity described in the specification and

shown in the assays in the specification would be useful in methods for treating an impairment of learning and/or memory. As generally known, the glutamatergic system in the brain is deeply involved in learning and memory processes in the hippocampus and cortex of rodents, but also of primates and humans. This can be proven by the memory deficits which are induced by systemic administration of NMDA-receptor antagonists (a specific glutamate receptor), such as phencyclidine, MK-801 or ketamine. Compounds which are able to facilitate glutamatergic neurotransmission can therefore enhance cognitive processes in diseases which have a dysfunction of the glutamatergic system. The learning and/or memory impairments – such as associated with Alzheimer's Disease and the other causes described in the specification – are related to such dysfunctional glutamatergic neurotransmission in the brain; see, e.g., the previously cited articles of Francis et al., *Int. J. Geriatric Psych.*, vol. 18, S15-21 (2003); and Francis et al., *J.Neurochem.*, vol. 60, no. 5, pp. 1589-1604 (1993). The postsynaptic glutamatergic processes are linked to the NO/cGMP/cGK/CREB pathway which is involved in synaptic plasticity and learning and memory processes on a molecular level; see, e.g., Puzzo et al., *J. Neurosci.*, vol. 25(29), pp. 6887-6897 (2005) (previously provided). Therefore, compounds enhancing cGMP levels in glutamatergic neurons, such as PDE9-inhibitors, are able to treat impairments of cognitive processes of memory deficits linked to a dysfunctional glutamatergic system, in general. The advantageous activity of the compounds for such use is not dependent on the cause of the impairment due to this general effect. The properties of PDE9-inhibitors for treating learning and/or memory impairments are shown by long-term potentiation experiments in-vitro and efficacy in the social recognition test in-vivo. Both, test paradigms are shown to be dependent on functional glutamatergic and/or NO/cGMP/cGK/CREB systems; see, e.g., attached Reymann et al., *Neuropharmacology*, vol. 52, pp. 24-40 (2007); and Puzzo, cited above. Taken together, compounds like PDE9-inhibitors showing efficacy in the mentioned test paradigms (i.e. long-term potentiation and social recognition test) would be reasonably expected to be of therapeutic benefit for treating learning and/or memory impairments linked to a dysfunctional glutamatergic system, as described by the current invention. In summary, therefore, there is a nexus between the type of physiological activity shown for the compounds (or readily verified by the assays provided in the specification) and the use for treating learning

and/or memory impairments. The newly provided Van der Staay reference further evidences the developing knowledge of the nexus directly between PDE inhibiting activity and pro-cognitive effects. For example, Van der Staay states (page 908): "Over the years, convincing experimental evidence has accumulated supporting the cognition-enhancing properties of several classes of PDE inhibitors." The reference then goes on to provide literature cites supporting this development particular to certain classes of PDE inhibitors over the years and culminates (page 917) with the finding that thier evidence showing the pro-cognitive effects of PDE9 inhibitors is "in concordance with previous studies demonstrating an enhancement of memory and neuronal plasticity by PDE5, PDE2 or PDE4 inhibitors."

It is argued in the Office action that the breadth of scope of the methods in claim 8 is not enabled because, for example, memory loss from traumatic amnesia or brain damage is permanent and cannot be rectified. Further, it is argued that many forms of dementia cannot be cured. There is no evidentiary basis for these statements on the record. However, even if supported, such would not support the rejection. A method for treating – as recited in the current claims – does not require a complete cure. For example, while a complete cure for Alzheimer's remains elusive, there are treatments available which slow or lessen the effects of the condition and/or prevent the worsening of the condition. And, certainly, there is a great deal of research looking to improve on the existing treatments. That, theoretically, there may be patients for whom treatment is not possible or not effective does not support a finding of non-enablement. Enablement for the current method of treatment claims does not require that every possible patient be successfully treated and certainly does not require that every possible patient be cured. Just because a treatment may not work in a specific instance does not refute that such a treatment can be generally accepted as reasonably expected to be successful in treating the condition generally. Enablement of the current claims only requires a reasonable expectation success in providing a patient with a treatment of their condition, i.e., some improvement in their condition. Based on the above-discussed knowledge in the art, one of ordinary skill in the art would have a reasonable expectation that the claimed compounds – due to their discussed PDE9 inhibiting activity and other assay activity discovered by applicants – would provide some beneficial treatment of patients with an impairment of learning and/or memory.

It is further argued in the Office action that there is no good physiological test for Alzheimer's disease and one must rely on assorted psychological tests. Applicants fail to see how this supports the case for non-enablement. The question is whether the available tests (whether physiological or psychological) provide a tool which is accepted in the art as indicative of improvement of the condition. The literature of record makes clear that the known psychological tests, such as the social cognition test, are accepted in the art for assessing impairment of learning and/or memory and, thus, the effectiveness of a treatment thereof; see, e.g., page 912 of Van der Staay. Of course, researchers are always looking for improved tests but that does not mean that the existing tests are not useful for assessing the condition. There is no basis on the record to support the PTO's position that the existing psychological tests, such as the social cognition test, are not effective for assessing impairment of learning and/or memory. To the contrary, the only evidence of record supports that such tests are relied on by those skilled in the art for such assessment. This is of particular relevance in the current context because applicants' describe in the specification that the compounds of their invention show an advantageous effect in an accepted animal model of the social cognition test (i.e., at pages 21-22). The specification here also describes why this test is useful for assessing impairment of learning and/or memory. The showing of the effectiveness of the compounds in an accepted animal model recognized in the art as useful for assessing impairment of learning and/or memory strongly supports enablement of the current claims.

Additionally, applicants' repeat, as follows, their comments on the Wands factors discussed in the previous Office action. These factors also support a finding of enablement. Applicants' assessment of these factors were not refuted in the Office action.

- Amount of Guidance – Applicants disagree with the previous allegation that they provided no guidance for carrying out the invention. As pointed out above, applicants point to the physiological activity and assays for determining such activity which have a nexus to use in carrying out the claimed methods.
- Unpredictability in the Art – Applicants respectfully disagree that any invention related to medicine is so unpredictable that non-enablement is presumed. No evidence is provided to support the PTO's allegation of unpredictability here. Further, the standard

for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).

- Number of Working Examples – The results of the assay at pages 17-19 showing PDE9A-inhibiting effect for the compounds of the invention are working examples. The results of the three following assays at pages 19-22 are also working examples of the physiological effect which has a nexus to use in carrying out the claimed methods.
- Nature of the Invention – The nature of the invention, as stated in the previous Office action, provides no implication of non-enablement.
- State of the Prior Art – The novelty of the invention (as indicated by the statement in the previous Office action) does not create any presumption of non-enablement. To the contrary, as pointed out above, the burden lies first with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims; see, e.g., MPEP §2164.04 citing Marzocchi et al., cited above. No such proof has been provided to refute the inventors' disclosure – and other supporting evidence – that the compounds would be useful in the claimed methods.
- Level of Skill in the Art – Applicants strongly disagree with the previous allegation that the level of skill of one of ordinary skill in this art is low. The level of skill is not an assessment of what has been accomplished in the effort. It is the level of the skill of those in the art working to solve the problem. That, historically, the disease or condition has been difficult to treat is not indicative of a low level of skill. To the contrary, the difficulty of treating the disease or condition – and the high impact of finding a treatment – means that those of very high skill level are working on the solution. Those working to find treatments as stated in the instant claims are Ph.D. level researchers at the highest level.
- Breadth of the Claims – The breadth of the claims was not addressed in the previous Office action but the breadth of claims here supports a finding of enablement. The compounds used for the methods are very well characterized and of a specific scope.
- Amount of Experimentation – The amount of experimentation required was not addressed

in the previous Office action. However, even if some further experimentation is required, such does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine experimentation to one of ordinary skill in the art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., In re Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404, stating: "Enablement is not precluded by the necessity for some experimentation ... . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation'." See also Ex parte Jackson, 217 USPQ 804 (Bd. Pat. App. 1982), stating: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."

For all of the above reasons, it is urged that one of ordinary skill in the art is adequately taught by applicants' specification – taken in view of the knowledge of one of ordinary skill in the art – how to carry out the claimed invention. Thus, the claims are enabled and the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/John A. Sopp/

John A. Sopp, Reg. No. 33,103
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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